

ORIGINAL ARTICLE

Diagnostic Accuracy of Urinary Spot Protein: Creatinine Ratio Versus 24 hours urinary Proteins in Patients with Preeclampsia

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ABSTRACT

Keywords:

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Background: In women with hypertensive disorders with pregnancy, the gold standard for diagnosis of significant proteinuria is 24-hour urine collection. However, 24-hour urine collection for measuring total proteinuria is time consuming, subject to collection error, requires good patient's compliance and usually done on an in-patient basis. **Objective:** The aim of the current work was to evaluate the accuracy of the spot urine Protein Creatinine ratio (PCR) in random urine samples as a predictor of significant proteinuria in women with hypertensive disorders with pregnancy. **Patients and methods:** This was an observational comparative prospective study conducted at Aswan University Hospital Obstetrics and Gynecology, Department during the period from April 2019 till September 2019. A total 90 pregnant women, recruited from either the antenatal clinic or the casualty, were included. **Results:** The random urinary protein/creatinine ratio was found to correlate significantly with the 24-hour total urinary albumin. It was shown that a receiver-operator characteristic (ROC) curve using the results of the 24-hour urine as the gold standard and then determining the sensitivity and specificity of the random protein/creatinine ratio with a range of cutoff values. A best cutoff value was at 0.45 and this yielded a sensitivity of as high as 82.1% and specificity of 87.5 %. These figures are quite acceptable and mean that this cutoff value can be used in clinical diagnosis and management. **Conclusion:** Random PCR could be used as a rapid, easy and reliable test for diagnosis of significant proteinuria in hypertensive disorders with pregnancy and can be used as an alternative to 24 hour urine collection.

INTRODUCTION

Hypertensive disorders complicate up to 10% of pregnancies worldwide, and considered as one of the greatest causes of

maternal and perinatal morbidity and mortality. It is classified according to presence or absence of proteinuria into four

categories: chronic hypertension, chronic hypertension with superimposed preeclampsia, preeclampsia and gestational hypertension. The diagnosis of preeclampsia

The patients with significant proteinuria have a significant reduction in the mean birth weight for gestational age compared to patients with hypertension alone due to intrauterine growth restriction. In contrast, in women with hypertension alone, the mean birth weight for gestational age is the same as that in normotensive women. Early detection and prompt management of patients with proteinuria is therefore beneficial to the patient and the fetus ⁽²⁾.

The gold standard for measuring proteinuria is a 24-hour urine sample for total protein; patients with hypertension have only <300 mg, those with mild preeclampsia have 300 mg to 5000 mg, and those with severe preeclampsia have >5000 mg of protein ⁽³⁾.

The 24-hour urine protein excretion method requires admission and it is costly and time consuming and its usefulness is limited to collection errors, storage difficulties, specimen handling, and poor patient compliance. Not only there is a delay in diagnosis due to waiting time, but also this method proves pointless when urgent delivery is required due to worsening maternal and fetal condition. Considering these issues, alternative methods for diagnosis of proteinuria in pregnancy have been thought off, which include dipstick method and spot urinary protein: creatinine ratio. The dipstick is inexpensive, easy to

PATIENT AND METHODS:

This was an observational comparative prospective study conducted at Aswan University Hospital Obstetrics and Gynecology Department during the period from April 2019 till September 2019. A total 90 pregnant women, recruited from either the antenatal clinic or the casualty, were included. All included women were initially diagnosed

is determined by the presence of hypertension accompanied by proteinuria, evident after 20 weeks' gestation ⁽¹⁾.

use, and rapid and the test can be done by paramedical health assistants including the patient herself ⁽⁴⁾.

For many years, proteinuria has been identified by screening random urine specimens using a semiquantitative chemical stick test. These methods are based on colour change of indicators. Such stick tests for protein have a detection limit in the range 200-250 mg/L and are subject to error, including false positive due to alkaline pH from infection or contamination with antiseptics, and false negative owing to very dilute urine and visual reading errors ⁽⁵⁾.

Random urine P/C ratio is a reliable indicator of significant proteinuria in preeclampsia and may be better at providing earlier diagnostic information than the 24-hour urine protein excretion with more accuracy than the urinary dipstick test ⁽⁶⁾.

The main potential benefits of this method is that in institutions where women with suspended PIH are hospitalized, women with insignificant proteinuria may be identified within a matter of hours and their follow up care handled on an outpatient basis ⁽⁷⁾.

Aim of the study is to evaluate the diagnostic accuracy of the random urinary protein/creatinine ratio for estimation of the significant proteinuria in preeclampsia in comparison to the gold standard 24-hour urinary protein.

to have mild to severe preeclampsia and admitted for further investigations.

An approval of the study was obtained from Aswan University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Inclusion criteria: Patients with new-onset hypertension defined as $\geq 140/90$ in two different measurements obtained at intervals

of more than 6 hours with positive urinary test strip for proteinuria of > 1+ corresponding to an albumin concentration of > 300 mg/l.

Exclusion criteria: Chronic renal or liver disease, diabetes mellitus, current or recent urinary tract infection, and chronic hypertension with pre-existing proteinuria.

Data collection: All women eligible to the study were subjected to baseline assessment including history, examination and investigations was done.

Full history taking: Name, age, residence, occupation, duration of marriage, special habits of medical importance, Symptoms suggesting of preeclampsia such as persistent headache, blurred vision, epigastric pain, and history of pre-existing hypertension, chronic renal disease or chronic liver disease, diabetes, SLE and history of Previous pregnancies complicated by preeclampsia. Calculating the gestational age from the first day of reliable LMP as follow (sure of date, regular at least 3 cycles, not on any hormonal contraception).

Full physical examination: pulse, blood pressure and temperature and respiratory rate. weight and height for calculating Body Mass Index. Pallor, Lower limb edema. Inspection of the abdomen for shape, contour, pigmentation and scars. Fundal level, fundal grip, umbilical grip and first pelvic grip. Auscultation of fetal heart sounds by pinard stethoscope or by sonicaid.

Investigations: Proteinuria in random urine sample by dipsticks, taking blood sample for checking hemoglobin level, platelet count, liver aminotransferases, serum creatinine and random blood sugar. A random urine sample was taken for checking both protein and creatinine levels, and the urinary protein-to-creatinine ratio (PCR) was calculated. 24-hour urine was collected for measuring total protein. I had informed the patient to urinate into the toilet when she gets up in the morning. Don't save the urine from her first time urinating. Flush this first specimen, but note the time. This is the start time of the 24-hour collection. Afterward, collect all urine in a special container (A brown plastic container is typically used). A special pan that fits in the

toilet or a urinal may be used to collect the urine for the next 24 hours. On the second day: she urinates into the container when she gets up in the morning. Cap the container and Keep it in the refrigerator or a cool place during the collection period. Label the container with her name, the date, the time of completion.

Patients had known that certain factors may affect the accuracy of 24-hour urine collection. These include: Forgetting to collect some of your urine. Going beyond the 24-hour collection period and collecting too much urine. Losing urine from the specimen container through spilling. Not keeping urine cold while collecting it. Acute stress. Vigorous exercise. Certain foods, such as coffee, tea, cocoa, bananas, citrus fruits, and vanilla.

Sample Size Justification:

Sample size was calculated using EpiInfo® version 6.0, setting the type-1 error (α) at 0.05 and the power ($1-\beta$) at 0.8. Data from a previous study⁽⁸⁾ showed that the positive predictive value of the urine dipsticks in detection of significant proteinuria was 59%, and that of the protein/creatinine ratio was 83%. Calculation according to these values produced a minimal sample size of 88 women. Therefore, approximately, 90 women with positive urine dipsticks are to be included in the study.

Statistical Methods:

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS®) for Windows® version 16.0. Data was expressed as range, mean and standard deviation (for numeric parametric variables), range, median and interquartile range (for numeric non-parametric variables), number and percentage (for categorical variables). Difference between variables of two groups was measured using independent student's t-test (for numeric parametric variables), Mann-Whitney's U-test (for numeric non-parametric variables), and continuity-corrected Chi-squared or Fischer's Exact (for categorical variables). Association between two variables was assessed using Pearson's correlation coefficient (for parametric variables) and Spearman's rank correlation coefficient (for non-parametric variables). Diagnostic

accuracy was assessed using terms of sensitivity, specificity, positive predictive value, negative predictive value and

likelihood ratios. P value < 0.05 was considered significant.

RESULTS:

mean gestational age was 33.67 weeks (± 3.49 , range 26-39). The median parity was 2. The mean body mass index (BMI) was 24.78 Kg/m² (± 1.09 , range 22 – 28.5) (Table 1).

In this study ninety pregnant women were recruited from either the antenatal clinic or the casualty. The mean age of included women was 28.46 (± 5.428 , range 19–42). The

	Range	Mean \pm SD
Age (Years)	19 – 42	28.49 \pm 5.428
Gestational Age (Weeks)	26 – 39	33.67 \pm 3.49
Parity	0 – 5	2 (1 – 4)*
BMI (Kg/m ²)	22 – 28.5	24.78 \pm 1.09

Table (1): Demographic Data of included women. Median (interquartile range) were used instead. BMI: “Body Mass Index”.

encountered in 10% only of the patients (Table 2).

The great percentage (90%) of the included patients had mild to moderate hypertension. However, severe hypertension was

Levels	Counts	% of Total
140/90	18	20.0%
150/90	18	20.0%
160/100	27	30.0%
180/100	18	20.0%
180/110	9	10.0%

Table (2): Blood Pressure levels in included women.

minority (7.7%) had severe proteinuria 3+ (Table 3).

This table shows that the majority of patients (66.7%) had mild proteinuria 1+, while the

Proteinuria by dipsticks	No. (%)
1+	60(66.7%)
2+	23(25.6%)
3+	7(7.7%)

Table (3): Proportion of proteinuria by dipsticks among included women.

ratio was 0.795 (± 0.608 , range 0.02–4.8) (Table 4).

This table shows that the mean for the 24-hour urinary protein was 595 mg (± 885 , range 178–5650). The mean for protein creatinine

Variable	Mean \pm SD	Range
24-hour protein (mg)	595 \pm 885	178–5650
PCR	0.795 \pm 0.608	0.02–4.8

Table (4): Protein-creatinine ratio (PCR) and 24-hour urinary protein among the studied cases. Total=90

correlation between total 24-hour urine protein and proteinuria detected by dipsticks in random urine samples ($r = 0.869$, $p < 0.001$) (Table 5).

There was a significant positive correlation between total 24-hour urine protein and PCR in random urine samples ($r = 0.875$, $p < 0.001$). There was a significant positive

		Proteinuria by Dipsticks	PCR in Random urine Sample
Total 24-Hour Urine Protein	r*	0.869 ***	0.875***
	P	< 0.001	< 0.001
	Significance	Highly Sig	Highly Sig

* Spearman's non- parametric correlation coefficient

Table (5): Correlation between total 24-hour urine protein and PCR in random. random urine samples and PCR ($r = 0.850$, $p < 0.001$) (Table 6).

There was a significant positive correlation between proteinuria detected by dipsticks in

		PCR in Random Urine Sample
Proteinuria by Dipsticks	r*	0.850***
	P	< 0.001
	Significance	Highly Sig

* Spearman's non- parametric correlation coefficient

Table (6): Correlation between proteinuria by dipsticks and PCR in random urine sample.

ROC curve of PCR in random urine sample was 83.3 denoting that PCR in random urine sample is a good predictor of significant proteinuria (Figure 1).

Receiver-Operator Characteristic (ROC) curve was constructed for total 24-hour urine protein, PCR in random urine sample as a predictor of significant proteinuria (≥ 300 mg per day). The area under the curve for the

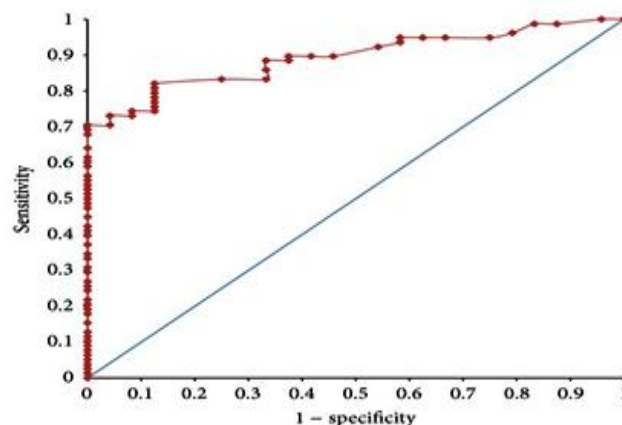


Figure (1): ROC Curve for PCR in random urine sample as a predictor of significant proteinuria a positive predictive value of 95.5% and a negative predictive value was 60%. This means that we can use this cutoff value in clinical diagnosis and management (Table 7).

In this study, it is concluded that a best cutoff value will be at 0.45 and this yielded a sensitivity of 82.1% and specificity of 87.5%.

Roc Curve					
Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
0.45	82.1	87.5	95.5	60.0	83.3

Table (7): Sensitivity, specificity, positive and negative predictive values.

Discussion:

The mean age of included women was 28.46 (± 5.428 , range 19–42). The mean gestational age was 33.67 weeks (± 3.49 , range 26-39). The median parity was 2. The mean body mass index (BMI) was 24.78 Kg/m² (± 1.09 , range 22 – 28.5)

This study shows a significant positive correlation between total 24-hour urinary protein and PCR in random urine samples ($r = 0.875$, $p < 0.001$). There was a significant positive correlation between Total 24-hour urine protein and proteinuria detected by dipsticks in random urine samples ($r = 0.869$, $p < 0.001$). There was a significant positive correlation between proteinuria detected by dipsticks in random urine samples and PCR ($r = 0.850$, $p < 0.001$).

Most studies had showed a strong correlation between spot PCR and 24-hour urine protein collection; however no consensus for specific PCR cut off value has been obtained. We believe that this test could be a reasonable alternative to clinicians in order to reduce their dependence on the 24-hour urine collection and suggest a cut-off of 0.02 g/mmol in the interests of patient safety. The advantage of PCR is not just it is a faster and more convenient test; it is the fact that all pregnant women with hypertension could be easily screened throughout pregnancy and up to delivery time. The sensitivities, specificities, positive and negative predictive values for PCR were calculated depending on the cut off used; we highlighted two clinically relevant cut-off values. A cut-off of 0.02 g/mmol (0.18 g/g) had sensitivity and a specificity of 97.6% and 44% respectively. The positive predictive value was 58% and negative predictive value was 96%. A cut off of 0.03 g/mmol (0.27 g/g) had sensitivity and specificity of 86% and 76% respectively, the positive predictive value was 73% and negative predictive value was 87% ⁽⁹⁾.

Fisher's exact test depicted a positive association between PCR with 24-hour urine protein, p value being less than 0.05. The area under curve was calculated as 0.87 95% CI (0.74-1.01), which was statistically significant. At cut off point of 0.3, sensitivity was 100%, specificity 90%, positive and negative predictive values 97.2% and 100% respectively. Random urine protein/ creatinine ratio (>0.3) is a reliable indicator of proteinuria >300 mg/day. It can be used as an alternative to 24-hour protein estimation ⁽¹⁰⁾.

In another study conducted on 509 out of 764 (255 subjects excluded due to various reasons) subjects revealed a p value of 0.0001, which is considered extremely significant, and an excellent correlation coefficient ($r = 0.9778$), (with a 95% confidence interval of 0.9700–0.9836,) for the spot urine protein-to-creatinine ratio (mg/mg) and 24-h urine protein (mg/day) was calculated by Pearson's method. The cut-off value of 0.285 results in a sensitivity of 100%, specificity of 99.02%, positive predictive value of 99%, and negative predictive value of 100%, with a 67% likelihood ratio ⁽¹¹⁾.

Another study conducted on a single group of 240 subjects found that the spot urine protein to creatinine value significantly correlates with 24-hour urine protein value, ($r=0.98$; $P<0.0001$). The protein to creatinine value for significant proteinuria was 0.285 with sensitivity of 100%, specificity of 99%, positive predictive value of 100% and negative predictive value of 99% ⁽¹¹⁾.

Also, they found a significant positive correlation in another study conducted in 100 antenatal women with pre-eclampsia, when 24 hour urinary protein and spot P/C ratio were correlated with $r= 0.59$ and P value being significant at < 0.001 , where all the observations were considered. A poor correlation was seen when 24 hour urinary

protein and urine visual dipstick were correlated with $r= 0.49$ and P value being 0.004. The area under the ROC curve was 0.939 (95% CI: 0.883, 0.995) $p < 0.001$ (significant). The optimal cut-off point was 0.315; this cut-off yielded a sensitivity of 84.8% and specificity 54.8%. But at the cut-off point of 0.2, sensitivity was 94% and specificity of 62%⁽¹²⁾.

CONCLUSION:

Random PCR could be used as a rapid, easy and reliable test for diagnosis of significant proteinuria in hypertensive disorders with pregnancy and can be used as an alternative to 24 hour urine collection.

Recommendation:

The protein/creatinine ratio should take its place as a both inpatient and outpatient procedure to evaluate albuminuria being so much easy, rapid and accurate

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